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Postradiotherapy Hypothyroidism: Radiation Dose Response and Chemotherapeutic Radiosensitization at Less Than 40 Gy

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To analyze our experience with iatrogenic hypothyroidism, we prospectively followed 84 patients, seen from 1984 to 1990, who had been diagnosed with either Hodgkin's disease (HD) or head and neck (H&N) carcinoma and subsequently treated with radiotherapy. Within these two diagnostic groups were subgroups whose treatment differed as to dose of therapeutic irradiation received or adjunctive use of chemotherapy. Approximately 50% of all patients and of each subgroup developed either clinical or subclinical hypothyroidism during follow-up. However, among the HD patients who received irradiation plus chemotherapy, a dose-response relationship below a threshold limit of dose received, probably 40 Gy, was observed.

KEY WORDS: **chemo-radiotherapy, head and neck carcinoma, Hodgkin's disease, hypothyroidism**

INTRODUCTION

Standard external radiotherapeutic techniques now in use in the treatment of many head and neck (H&N) carcinomas as well as in Hodgkin's disease (HD) necessitate exposure of the thyroid gland to external radiation, typically in the order of 20–70 Gy. Despite innovative efforts to devise protective coverings for the thyroid, the locations of the targeted carcinomatous or lymphomatous masses may prevent the optimal use of midline shielding. This is a well-recognized problem stemming from the use of mantle irradiation for HD [1].

Both clinical and subclinical thyroid abnormalities, appearing as late complications of appropriate and life-prolonging treatment, have been frequently reported. Hypothyroidism, the more common disorder, was recently diagnosed in 31–78% of therapeutically irradiated HD patients, whereas clinical hypothyroidism had an incidence of 6–25% [2]. These abnormalities appeared up to 25 years after the original treatment, and the longer the posttreatment time, the higher the likelihood of evolution to a hypothyroid state. In irradiated H&N patients, hypothyroidism is typically reported in 10–45% of patients [3,4] and in a recent study was identified in 26% of patients [3], most of whom manifested a subclinical variety.

Thresholds are uncertain; however, doses to the neck exceeding 30 Gy were associated with hypothyroidism among one cohort of patients at follow-up times from 5–34 years after treatment [4]. We studied the incidence of hypothyroidism in a cohort of 84 patients with either HD or H&N carcinoma, irradiated and followed from 1984 to 1990, and the influence of chemotherapy on hypothyroid state induction.

MATERIALS AND METHODS

Between 1984 and 1990 in the Department of Oncology at Rambam Medical Center, we administered radiother-

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apy with or without chemotherapy to 84 patients with either H&N epithelial carcinoma or HD. The two diagnostic categories were equally represented; 43 patients had H&N and 41 had HD. The age range was wide—14–71 years—and the sex distribution was 51 males and 33 females.

All of the 43 H&N patients received 46–70 Gy irradiation using lateral opposed cervical and "straight-on" supraclavicular fields. Of these, 30 received only radiotherapy; 13 patients with either recurrences or locoregionally advanced disease additionally received one of the platinum-based chemotherapy regimens: cisplatin/5-fluorouracil or cisplatin/methotrexate/bleomycin.

Of the 41 HD patients, eight received only radiotherapy in doses of 40–45 Gy, whereas the remaining 33 received standard chemotherapy: nitrogen mustard, oncovin, procarbazine, and prednisone [MOPP], alternating with Adriamycin, bleomycin, vinblastine, dacarbazine [ABVD], and consolidation radiation therapy in the range of 20–40 Gy. Consolidation was given at three different dose levels, depending upon disease bulk. Ten patients with bulky disease received 38–40 Gy; 15 received 30–36 Gy and eight received only 20–26 Gy. Radiotherapy was given using the "mantle" or "mini-mantle" technique, which included the entire thyroid gland, although a midline block was generally applied. For both H&N and HD groups, thyroid exposure ranged from 20–70 Gy.

Follow-up thyroid testing began 1–6 years posttreatment. Clinical hypothyroidism was defined as a TSH >5 uu/ml (lab normal 0.04–5.0 uu/ml, measured by ultrasensitive radioimmunoassay) and a T4 value <0.8 uu/dl (lab normal 0.8–2.0 pmol/l, by radioimmunoassay), in conjunction with classical signs such as slow reflexes, long-standing constipation and bradycardy. Subclinical hypothyroidism included patients with the above TSH abnormalities but were asymptomatic.

RESULTS

Within 1–6 years after treatment, 38 (45%) of our 84 H&N or HD patients manifested hypothyroidism at either the clinical (9 patients:25%) or subclinical (29 patients:75%) level. Breakdown by major diagnosis revealed that 47% of the H&N patients and 44% of HD patients became hypothyroid (Table I).

All 43 H&N patients received 46–70 Gy or irradiation and six of these also received chemotherapy. Whether or not treated chemotherapeutically, this diagnostic group manifested an incidence of 50% hypothyroidism. The 41 HD patients may be divided into two groups: those who received only radiotherapy at a dose ≥40 Gy, and those who received chemotherapy initially, followed by consolidating radiotherapy at lower dose ranges of 20–40 Gy.

The lower dose and chemotherapeutically treated group was comprised of three subgroups who were differentially irradiated as to dose according to the size of tumor at the time of diagnosis and/or the residual disease after chemotherapy. Among those three dosage subgroups, there were differing incidences of clinical/subclinical hypothyroidism, ranging from 12.5% in the least irradiated group, to 40% in the intermediate range of irradiation, to 70% in those who received 30–40 Gy (Table II).

TABLE I. Hypothyroidism Subsequent to Treatment for H&N and HD

Diagnosis	Treatment	No. of pts.	Hypothyroid incidence
H&N	Radiotherapy 46–70 Gy	30	
		}	47%
	Radiotherapy 46–70 Gy + chemotherapy	13	
HD	Radiotherapy 40–45 Gy	8	
		}	44%
	Radiotherapy 20–40 Gy + chemotherapy	33	

TABLE II. Hypothyroidism in HD Patients After 20–40 Gy Irradiation + Chemotherapy

Dose	No. of pts.	Hypothyroidism incidence
38–40 Gy	10	7 (70%)
30–36 Gy	15	6 (40%)
20–26 Gy	8	1 (12.5%)

DISCUSSION

Iatrogenic thyroid disorders are a known risk associated with any radiotherapeutic or radiodiagnostic exposure of the thyroid gland. The spectrum of these disorders ranges from cancer itself to relatively benign conditions. Thyroid carcinoma is associated with irradiation during childhood, formerly given for such innocent conditions as thymic or tonsillar enlargement as well as skin disorders [5]. Other sequelae, not life-threatening but still of concern, include Jodbasedow hyperthyroidism occurring after diagnostic radiography with radioactive iodine [6]. Transient nonsupportive thyroiditis has been seen after "internal radiotherapy" using radioactive iodine therapy for either diffuse or toxic nodular goiter (Grave's disease) [6], sometimes with persisting hypothyroidism. Attempts have been made to quantify a dose-response relationship for internal radiation and subsequent hypothyroidism [7]; however, it has been less than clear that such a relationship exists for externally administered radiotherapy.

The finding of either clinical or subclinical hypothyroidism in ~50% of our externally irradiated H&N and HD patients is commensurate with that of some other

centers [3,4]. This finding was consistent at doses above 40 Gy whether or not the patients received chemotherapy. For H&N patients, risk factors that significantly influenced a high incidence of hypothyroidism included, aside from high radiation dose and no shielding, cervical surgery (including thyroidal lobectomy), and time from therapy [3,8–11]. The contribution of chemotherapy given prior to neck irradiation on the development of hypothyroidism is still unsettled [3,9].

A group of 33 patients who received less than 40 Gy manifested a dose-dependent relationship between the amount of irradiation received and the incidence of subsequent hypothyroidism. This group differed from the larger group in three ways: all were HD patients, all had had lower dose irradiation [<40 Gy], and all had received chemotherapy with this low dose irradiation. Since HD patients who underwent higher dose radiotherapy had a hypothyroid incidence identical to that of H&N patients at the same dose, the singularity seems not to be associated with the underlying diagnosis. Likewise, chemotherapy seems not to have made the difference at higher doses of radiotherapy (46–70 Gy), when the incidence of hypothyroidism with or without chemotherapy is a uniform 47%. However, at lower doses of radiotherapy (38–40 Gy), when a 70% incidence of hypothyroidism was found, chemotherapy may well have acted as a radiosensitizer. The 40% incidence of hypothyroidism at still lower doses (30–36 Gy), when given in conjunction with chemotherapy, also suggests an enhancement of radiotherapeutic effect on the thyroid, particularly on patients >16 years of age and of the female gender [12]. The role of ethiodized lymphangiographic contrast media on hypothyroidism induction remains unclear [12,13].

Literature data suggest that the thyroid in children may be more sensitive to radiation as compared with older age groups [14,15]. However, other reports on large studies could not demonstrate a significant influence of age [8]. Because of our small numbers, we could not make a valid interpretation of the influence of age in our material.

In conclusion, it seems that dose response with respect to subsequent hypothyroidism comes into play even at doses below 40 Gy irradiation. Although we may be able to assume an advantage to the thyroid status of these less intensively irradiated patients, there is no doubt that thyroid function testing should be a routine part of the follow-up in all patients who have undergone radiotherapy to the area of the thyroid, even at low doses. Innoviate and safer shielding methods are necessary to reduce iatrogenic thyroid dose without compromising treatment efficacy.

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REFERENCES

1. Peerboom PF, Hassink EAM, Melkert R, et al.: Thyroid dysfunction 10–18 years after mantle field irradiation for Hodgkin's disease. Eur J Cancer 10:1716–1718, 1991.
2. Bookman MA, Longo DI: Concomitant illness in patients treated for Hodgkin's disease. Cancer Treat Rev 13:77–111, 1986.
3. Grande C: Hypothyroidism following radiotherapy for head and neck cancer: Multivariate analysis of risk factors. Radiother Oncol 25:31–36, 1992.
4. Kaplan MM, Garnick MB, Gelber R, et al.: Risk factors for thyroid abnormalities after neck irradiation for childhood cancer. Am J Med 74:272–280, 1983.
5. Wittes RE: Endocrine system. In Wittes RE [ed]: "Oncologic Therapeutics 1991–1992." Philadelphia: Lippincott, 1991, p 221–224.
6. Schroeder SA, Krupp MA, Tierney LM, et al.: Current medical diagnosis and treatment. Prentice-Hall International, 1990.
7. Kalistratova VS: The relation of non-stochastic effects to the radiation dose of the human thyroid gland. Vestnik Akademii Meditinskikh Nauk Sssr 43–47, 1992.
8. Tami TA, Gomez P, Parker GS, et al.: Thyroid dysfunction after radiation therapy in head and neck cancer patients. Am J Otolaryngol 13:357–362, 1992.
9. Weissler MC, Berry BW: Thyroid-stimulating hormone levels after radiotherapy and combined therapy for head and neck cancer. Head Neck 13:420–423, 1991.
10. Liening DA, Duncan NO, Blakeslee DB, et al.: Hypothyroidism following radiotherapy for head and neck cancer. Otolaryngol Head Neck Surg 103:10–13, 1990.
11. Buisset E, Leclerc L, Lefebvre JL, et al.: Hypothyroidism following combined treatment for hypopharyngeal and laryngeal carcinoma. Am J Surg 162:345–347, 1991.
12. Hancock SL, McDougall IR, Constine LS: Thyroid abnormalities after therapeutic external radiation. Int J Rad Oncol Biol Phys 31:1165–1170, 1995.
13. Constine LS, Donaldson SS, McDougall IR: Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. Cancer 53:878–883, 1984.
14. Smith RE, Adlen RA, Clark P, et al.: Thyroid function after mantle irradiation in Hodgkin's disease. JAMA 245:46–49, 1981.
15. Green DM, Brecken ML, Yakar D, et al.: Thyroid function in pediatric patients after neck irradiation for Hodgkin's disease. Med & Ped Oncol 8:127–136, 1980.